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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/841,744	04/24/2001	Jorge F. DiMartino	12636-891	5759

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 05/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/841,744	DIMARTINO, JORGE F.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,9-14 and 16-38* is/are pending in the application.

4a) Of the above claim(s) *29 and 31-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,9-14,16-28 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/25/04*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *12/17/03*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Request for Continued Examination (RCE) filed February 25, 2004 under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

Status of the Claims

2. Claims 1, 4, 9-14 and 16-38 are pending.

Applicants' amendment filed on February 25, 2004 is acknowledged, and applicants' response has been fully considered. Claims 1, 4, 9-12, 19, 23, 24 and 28 have been amended, and claims 3, 5 and 8 have been cancelled. Claims 29 and 31-38 are non-elected inventions and are withdrawn from consideration. Thus, claims 1, 4, 9-14, 16-28 and 30 are examined.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

3. The previous rejection of claim 8 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's cancellation of the claim in the amendment filed February 25, 2004.

4. The previous rejection of claims 1, 4, 8-14, 16-28 and 30 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicant's amendment to the claim, applicant's cancellation of the claim, and applicant's response at pages 9-10 in the amendment filed February 25, 2004.

Claim Objections

5. Claim 28 is objected to because the claim contains recitation of non-elected anti-neoplastic agents.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 4, 9-14, 16-28 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a patient having a cancer with a combination therapy comprising administering decitabine or 5-azacytidine as a DNA methylation inhibitor at a dose 1-50 mg/m^2 per day in combination with a therapeutically effective amount of a specific histone deacetylase (HDA) inhibitor such as depsipeptide, phenylbutyrate or arginine butyrate, optionally with an antibiotic agent as an anti-neoplastic agent, does not reasonably provide enablement for a method of treating a patient having a cancer with a combination therapy comprising administering decitabine or 5-azacytidine as a DNA methylation inhibitor at a dose 1-50 mg/m^2 per day in combination with a therapeutically effective amount of a histone deacetylase (HDA) inhibitor of hydroxamic acid, cyclic peptide, benzamide, butyrate and depudecin, optionally with an antibiotic agent, wherein the structure of hydroxamic acid, cyclic peptide, benzamide or butyrate is not defined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1, 4, 9-14, 16-28 and 30 encompass a method of treating cancer with a combination therapy comprising administering decitabine or 5-azacytidine in combination with a histone deacetylase inhibitor (claims 1, 4, 9-14, 16-27), optionally with an antibiotic agent (claims 28 and 30). The specification, however, only discloses cursory conclusions without data supporting the findings, which state that the invention provides a method of treating a disease such as cancer using a combination therapy including a DNA methylation inhibitor and a histone

deacetylase inhibitor, which triggers cancer cell death through reestablishment of intrinsic death mechanism of cells such as growth arrest, differentiation and apoptosis through activation of genes selectively silenced in cancer cells, and the cancer cells sensitized by such a combination die quickly or become more prone to cell death signals sent by administration of conventional anti-neoplastic agents (page 8, lines 8-18). There are no indicia that the present application enables the full scope in view of a method of treating various cancers using the combination therapy of decitabine or 5-azacytidine and a histone deacetylase inhibitor as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding histone deacetylase inhibitors including various hydroxamic acids, cyclic peptides, benzamides, and butyrates, which are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

There are no working examples indicating the claimed methods in association with the variants. The specification has not demonstrated the effect of decitabine or 5-azacytidine in

combination with various hydroxamic acids, cyclic peptides, benzamides, butyrates and depudecin in the treatment of various cancers.

(3). The state of the prior art and relative skill of those in the art:

The related art, e.g., Zhu *et al.* (Cancer Research 61, 1327-1333 (2001)) indicates histone deacetylase (HDA) inhibitors such as depsipeptide (FR901228) and trichostatin A induce apoptotic cell death, and this induced apoptosis is greatly enhanced in the presence of the DNA methyltransferase inhibitor, 5-aza-2'-deoxycytidine (decitabine); and the references provided by applicants (see IDS filed February 25, 2004) indicate DNA methylation is associated with various cancers, and synergistic antineoplastic effect of 5-aza-2'deoxycytidine and depsipeptide against several tumor cells (post filing date references). However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific teachings on treating conditions such as dose for treating various cancers using decitabine or 5-azacytidine in combination with a specific histone deacetylase inhibitor and the effect of the combination therapy to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method of treating cancer with a combination therapy comprising administering a DNA methylation inhibitor such as decitabine or 5-azacytidine and a histone deacetylase inhibitor, optionally with an antibiotic agent. However, the treating conditions such as the dose of a specific HDA inhibitor in the combination therapy for treating various cancers, and the effects of various HDA inhibitors in the treatment are not adequately described in the specification, thus, the invention is highly unpredictable regarding the outcome of the treatment, e.g., Parsons (WO 98/55449) discloses an HDA inhibitor, trichostatin (TSA) or

HC-toxin (a cyclic peptide) is tumor-selective in vitro, but it is inactivated by culture cells and lacks antitumor activity in vivo even at high doses (page 4, line 12-page 5, Example 1, Table 2; example 6, Fig. 6); Yoshida et al., (J. Biol. Chem. 265, 17174-17179 (1990)) indicates n-butyrate is noncompetitive inhibitor of histone deacetylase and has other biological effects on cultured mammalian cells such as suppression of the characteristic phenotypes of transformed cells, induction of differentiation in many tumor cell lines, and specific inhibition of the cell cycle at the G1 and G2 phases, thus a more specific and potent inhibitor of histone deacetylase is necessary for analysis of its effect (page 17174, right column).

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of treating cancer with a combination therapy comprising administering decitabine or 5-azacytidine in combination with a histone deacetylase inhibitor, optionally with an antibiotic agent. The specification indicates methylation of DNA or deacetylase of histone plays an important role in regulation of gene expression, and the disease such as cancer is related to aberrant silencing of gene expression, thus, a combination therapy of a DNA methylation inhibitor such as decitabine and 5-azacytidine, and a histone deacetylase inhibitor can be used to treat cancer through reestablishment of gene transcription (pages 1, 15-18, 20-21); and further asserts that various cytidine analogs or derivatives can be used as a DNA methylation inhibitor and various histone deacetylase inhibitors such as hydroxymic acids, cyclic peptides, benzamides, butyrates and depudecin can be used as a histone deacetylase inhibitor (pages 8-9). However, the specification has not demonstrated the effect of the combination therapy using various histone deacetylase inhibitors although the doses of depsipeptide,

phenylbutyrate and arginine butyrate have been indicated (pages 11 and 37). Moreover, the specification has not shown the treating conditions such as the dosage for various histone deacetylase inhibitors other than depsipeptide, phenylbutyrate and arginine butyrate in the combination therapy, and there are no working examples indicating the effect of combination therapy in the claimed method. Although certain histone deacetylase inhibitors such as trichostatin (TSA) or HC-toxin is tumor-selective in vitro, it lacks antitumor activity in vivo, and the effect of n-butyrate as a histone deacetylase inhibitor in vivo is not clear due to lack of specificity (see the section of unpredictability), furthermore, the specification fails to provide sufficient teachings on the treatment of various cancers and the effect of using combination therapy, thus it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the combination therapy using decitabine or 5-azacytidine with various histone deacetylase inhibitors in the treatment of cancer.

(6). Nature of the Invention

The scope of the claims encompasses using decitabine or 5-azacytidine with various histone deacetylase inhibitors in the combination therapy for treating various cancers, but the specification has not demonstrated the effect of combination therapy using decitabine or 5-azacytidine with various histone deacetylase inhibitors. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, there are working examples demonstrating the claimed method, the effect of various histone deacetylase inhibitors in the treatment is unpredictable, and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of combination

therapy using decitabine or 5-azacytidine in combination with a histone deacetylase inhibitor of hydroxamic acid, cyclic peptide, benzamide, butyrate and depudecin in the treatment of various cancers.

In response, applicants indicate in the previous Office Action, claims 1, 4, 9-14, 16-28 and 30 are rejected under 35 U.S.C. 112, first paragraph, for not enabling a method of treating all cancers, and during a telephone interview on December 17, 2003 (see interview summary), the issue of enablement of the claimed method for treating cancer was discussed, and applicants agree to provide references indicating DNA methylation is associated with various cancers, and these references show that one of ordinary skill in the art would understand the relationship between DNA hypermethylation and cancer, thus in view of applicant's teachings, the claimed method for treating cancer using a combination of a DNA methylation inhibitor and a HDA inhibitor is enabled (pages 7-9 of the response). The response has been fully considered, regarding the treatment of various cancers, the argument is found persuasive, thus the rejection is withdrawn. However, regarding using various HDA inhibitors in the combination therapy for treating cancers, the scope of the claims is not fully enabled because the specification has not indicated the treating conditions such as the dosage for various histone deacetylase inhibitors other than depsipeptide, phenylbutyrate and arginine butyrate in the combination therapy, nor has demonstrated the effect of the combination therapy using various histone deacetylase inhibitors, which is encompassed by the claim. Furthermore, the in vivo effect of the histone deacetylase inhibitor in the treatment of cancer is not predictable (see the section of unpredictability), thus it is necessary to carry out further experimentation to assess the effect of decitabine or 5-azacytidine in combination with a histone deacetylase inhibitor of hydroxamic acid, cyclic

peptide, benzamide, butyrate and depudecin in the treatment of cancer as indicated in the section above.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is indefinite because of the use of the term "osteogenic and other sarcoma". The term cited renders the claim indefinite, it is not clear what other sarcoma are.

Conclusion

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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CHK

Chih-Min Kam, Ph. D.
Patent Examiner

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May 12, 2004